DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 103951/0

SEP 17 2001

George Morstyn, Ph.D.
Amgen, Incorporated
One Amgen Center Drive
Thousand Oaks, CA 91320-1789

Dear Dr. Morstyn:

Your biologics license application for darbepoetin alfa is approved effective this date. Amgen, Incorporated, Thousand Oaks, California, is hereby authorized to introduce or deliver for introduction into interstate commerce, darbepoetin alfa under Department of Health and Human Services U.S. License No. 1080.

Darbepoetin alfa is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis. Under this authorization, you are approved to manufacture darbepoetin alfa at your facility in Thousand Oaks, California. Final formulated drug product will be filled, labeled, and packaged at your facility in [ ] and the labeled and packaged vials of drug product will be shipped to your facility in [ ] for distribution. In accordance with approved labeling, your product will bear the proprietary name Aranesp, and will be marketed in two formulations, containing either Albumin (Human) or Polysorbate 80, in the following strengths: 25 µg/mL, 40µg/mL, 60µg/mL, 100µg/mL and 200µg/mL.

The dating period for darbepoetin alfa containing Albumin (Human) shall be [ ] months from the date of manufacture when stored at 2-8°C. The dating period for darbepoetin alfa containing Polysorbate shall be [ ] months from the date of manufacture when stored at 2-8°C. The bulk drug substance may be stored for up to [ ] The date of manufacture shall be defined as the date of final sterile filtration of the final formulated product. Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots. The stability protocol in your license application, as amended on September 13, 2001, is considered approved for the purpose of extending the expiration dating period of your drug substance and drug product as specified in 21 CFR 601.12. Please submit the final stability protocol containing the revisions outlined in your September 13, 2001 amendment in your annual report.

You are not currently required to submit samples of future lots of darbepoetin alfa to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

Any changes in the manufacturing, testing, packaging or labeling of darbepoetin alfa, or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have not fulfilled the requirements of 21 CFR 601.27. On the basis of your commitment described in item 5 below, we are deferring the submission of your pediatric studies, under 21 CFR 601.27(b), until [ ].

We acknowledge your agreement to conduct post-marketing studies and to provide additional information as described in your letters of August 17 and 23, 2001, and as outlined below:

1. To set quantitative limits for the "Mapping of N-glycosylated Sialylated Oligosaccharides" (Analytical Metho[ ] following manufacture of the first 30 commercial lots. The limits will be set as the[ ]based on analysis of the data.

2. To develop and evaluate improved immunogenicity assays for detecting antibodies to darbepoetin alfa. The results of your evaluation and validation data for any improved assays will be submitted by[ ]

3. To analyze, using an improved and validated assay, archived serum samples on 500 chronic renal failure (CRF) patients who have been treated with the Albumin formulation and on 1000 CRF patients who have been treated with the Polysorbate formulation. The results, with revised labeling if applicable, will be submitted by[ ]If antibodies to darbepoetin alfa are detected, Amgen will submit data establishing whether these antibodies cross-react with native erythropoietin.

4. To evaluate the safety of darbepoetin alfa in African American patients. Four hundred African American CRF patients receiving hemodialysis will be randomized to receive either darbepoetin alfa or another recombinant human erythropoietin. The final study protocol will be submitted to CBER by[ ] Patient accrual will be initiated by[ ]and completed by[ ] The study will be completed by[ ]and the final clinical study report, with revised labeling if applicable, will be submitted to FDA by[ ]

5. To assess the pharmacokinetics, safety and efficacy of darbepoetin alfa in pediatric patients. A pediatric study is[ ] Patient accrual will be completed by[ ] the study completed by[ ]and, a final clinical study report and applicable labeling submitted to FDA by[ ]

We also acknowledge your agreement to conduct additional validation studies as described in your response to the Agency's pre-approval inspectional observations, including:

6. Validation of the [ ] step (with incorporation of the validated [ ] into the manufacturing procedure [ ] prior to resuming purified bulk production);

7. Validation of the [ ] and,

8. Validation of [ ] reuse.

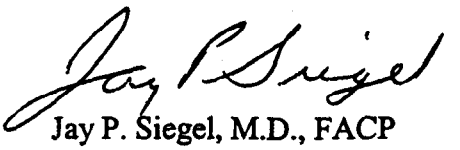
For administrative convenience, we request that you provide the completed validation reports in your next annual report submitted under 21 CFR 601.12.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 2567. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 or Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2567 or Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,



Jay P. Siegel, M.D., FACP
Director
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Research and Review
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